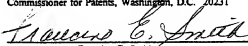


U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		01130/HG
FORM PTO-1100 (REV. 10-04)	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	PRIORITY DATE CLAIMED
INTERNATIONAL APPLICATION NO. PCT/JP99/05239	INTERNATIONAL FILING DATE 24 September 1999	09/787164
TITLE OF INVENTION Eyedrops for promoting lacrimal secretion or treating keratoconjunctival disorders containing natriuretic peptide as active ingredient		
APPLICANT(S) FOR DO/EO/US Katsuhiko NAKATA, Masatsugu NAKAMURA		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.		
2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.		
3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).		
4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.		
5. <input type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ul style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 		
6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).		
7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ul style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 		
8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).		
9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).		
10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).		
Item: 11. to 16. below concern document(s) or information included:		
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.		
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.		
13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.		
14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.		
15. <input type="checkbox"/> A substitute specification.		
16. <input type="checkbox"/> A change of power of attorney and/or address letter.		
16. <input checked="" type="checkbox"/> Other items or information: Copy of :		
(i) NOTICE PCT/IB/308		
(ii) INFORMATION PCT/IB/332		
(iii) WO 00/18422, title page only, the 18-month publication of PCT/JP99/05239		
(iv) English-language Int'l Search Report PCT/ISA/210		
(v) English-language Int'l. Prel. Exam. Report PCT/IPEA/409		
ASSIGNMENT INFORMATION FOR PUBLICATION: (SEE ATTACHED)		
SANTEN PHARMACEUTICAL CO., LTD. 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku Osaka-shi, Osaka 533-8651 Japan		
Express Mail Mailing Label No.: EL 759 977 444 US		Date of Deposit: March 14, 2001
I hereby certify that this paper and any papers identified herein is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231		
 Francine E. Smith		

CALCULATIONS PTO USE ONLY

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

JC08 Rec'd PCT PTO **14 MAR 2001**

Search Report has been prepared by the EPO or IPO \$860.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) \$690.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482)
but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$750.00Neither international preliminary examination fee (37 CFR 1.482) nor
international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$1000.00International preliminary examination fee paid to USPTO (37 CFR 1.482)
and all claims satisfied provisions of PCT Article 33(2)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$ 860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

\$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	10 - 20 =	0	x 18.00
Independent claims	3 - 3 =	0	x 80.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ 270.00

\$

\$

\$

TOTAL OF ABOVE CALCULATIONS =

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must also be filed (Note 37 CFR 1.9, 1.27, 1.28).

\$

SUBTOTAL =

\$ 860.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(f)).

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+

TOTAL NATIONAL FEE =

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Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
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\$

TOTAL FEES ENCLOSED =

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Amount to be:	\$
refunded	
charged	\$

a. ☒ A check in the amount of \$ 860.00 to cover the above fees is enclosed.b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
overpayment to Deposit Account No. 06-1378. A duplicate copy of this sheet is enclosed.NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR
1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

01933

PATENT & TRADEMARK OFFICE

FRISHAUF, HOLTZ, GOODMAN, LANGER & CRICK, P.C.
767 Third Avenue - 25th Floor
New York, NY 10017-2023

Tel. No. (212) 319-4900

Fax No. (212) 319-5101

Date: March 14, 2001

SIGNATURE

Herbert Goodman

NAME

17,081

REGISTRATION NUMBER

HG/fs

09/787164

JC08 Rec'd PCT/PTO 14 MAR 2001

Attorney Docket No. 01130/HG

**IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE**

Applicant(s): Katsuhiko NAKATA et al

Serial No. : (U.S. National Phase of
PCT/JP99/05239 filed
September 24, 1999)

Filed : Concomitantly Herewith

For : EYEDROPS FOR PROMOTING
LACRIMAL SECRETION OR
TREATING KERATOCONJUNCTIVAL
DISORDERS CONTAINING
NATRIURETIC PEPTIDE
AS ACTIVE INGREDIENT

Express Mail Mailing Label

No.: EL 759 977 444 US

Date of Deposit: March 14, 2001

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deposited with the United States Postal
Service "Express Mail Post Office to
Addressee" service under 37 CFR 1.10 on the
date indicated above and is addressed to the
Assistant Commissioner for Patents,
Washington, D.C. 20231

Francine E. Smith
Francine E. Smith

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and the necessary petition for extension of
time is not filed concurrently herewith,
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requisite extension of time, and to the
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extension fee, or any other fee
required in connection with this Paper
to Account No. 06-1378.

**PRELIMINARY AMENDMENT FILED
CONCOMITANT WITH APPLICATION**

Assistant Commissioner for Patents

S I R :

Please amend the application as follows.

IN THE SPECIFICATION:

Page 1, after the title and above line 1 (which is
"Technical Field") insert the following

--This application is the United States National Phase
Application under 35 USC 371 of International Application
PCT/JP99/05239 (not published in English) filed September 24,
1999.--

Page 7, replace the four paragraphs on lines 11 through 18 with the following four paragraphs:

--SM(D-T): Schirmer value in the eye to which the drug was administered (left eye) T hours after administering the drug

--SM(D-O): Schirmer value in the eye to which the drug was administered (left eye) before administering the drug

--SM(V-T): Schirmer value in the eye to which the vehicle was administered (right eye) T hours after administering the vehicle

--SM(V-O): Schirmer value in the eye to which the vehicle was administered (right eye) before administering the vehicle--.

IN THE CLAIMS:

1. (Amended) Eyedrops for promoting lacrimal secretion containing a natriuretic peptide as an active ingredient in an ophthalmic vehicle.

2. (Amended) Eyedrops for treating a keratoconjunctival disorder containing a natriuretic peptide as an active ingredient in an ophthalmic vehicle.

Please add the following claims 4-10.

4. (New) A method of treating a person having a keratoconjunctival disorder comprising administering an effective amount of a natriuretic peptide to at least one eye of said person.

5. (New) The method of claim 3 wherein said keratoconjunctival disorder is dry eye.

6. (New) The method of claim 3 wherein said keratoconjunctival disorder is corneal erosion.

7. (New) The method of claim 3 wherein said keratoconjunctival disorder is corneal ulcer.

8. (New) The method of claim 4 wherein said natriuretic peptide is an atrial natriuretic peptide.

9. (New) The method of claim 4 wherein said natriuretic peptide is a brain natriuretic peptide.

10. (New) The method of claim 4 wherein said natriuretic peptide is a C-type natriuretic peptide.

REMARKS

Claims 4-7 are supported by the disclosure starting in the upper portion of page 4 of the specification and original claims 2 and 3.


Claims 8-10 are supported by the disclosures on page 4 and pages 7-8.

The amendment to claims 1 and 2 is supported by the disclosure on page 4, lines 3 and 4 from the bottom.

The amendment to page 7 is the obvious correction of an obvious error taking into consideration the disclosure on page 6, lines 14-16.

The amendments to page 1, page 7 and to original claims 1 and 2 are shown in the attached marked up copy of page 1, page 7 and of original claims 1 and 2.

Respectfully submitted,


HERBERT GOODMAN
Reg. No. 17,081

Frishauf, Holtz, Goodman,
Langer & Chick, P.C.
767 Third Avenue - 25th Floor
New York, NY 10017-2023
Telephone: (212) 319-4900
Facsimile: (212) 319-5101
HG/fs

Specification

Eyedrops for Promoting Lacrimal Secretion or Treating Keratoconjunctival

Disorders Containing Natriuretic Peptide as Active Ingredient

This application is the United States National Phase Application under 35 USC 371 of International Application PCT/JP99/05239 (not published in English) filed September 24, 1999.

Technical Field

The present invention relates to eyedrops for promoting lacrimal secretion or treating keratoconjunctival disorders containing a natriuretic peptide as an active ingredient.

Background Art

A lacrimal fluid, which has a mechanism to retain wettability on living bodies, covers cornea and conjunctiva (keratoconjunctiva), retains wettability and prevents them from drying. The lacrimal fluid works as a lubricant protecting the keratoconjunctiva from stimulation by blinking and contributes to retaining smoothness of the corneal surface. The lacrimal fluid has bacteriostasis, prevents infection from bacteria, fungus, virus and the like, supplies oxygen and a variety of nutrition to the cornea and removes a carbon dioxide gas and metabolites. When the keratoconjunctiva is disordered, the lacrimal fluid plays a role to dilute and remove disordering stimuli, and works to carry liquid components such as epidermal growth factors participating in wound healing and hematocyte components such as fibronectin to disordered sites. That is, the lacrimal fluid participates in adjusting wound healing as well as retaining keratoconjunctival epithelial cells. Thus, it is known that the lacrimal fluid, though its amount is very

was measured from the fold.

Three minutes before measuring the amount of the lacrimal fluid, a 0.4% ophthalmic solution of oxybuprocaine hydrochloride (10 μ l), which is a local anesthetic, was instilled into both eyes once.

Results

The action of the solution of the test drug on the rate of the lacrimal secretion at a time of T hours after the instillation is represented by the increment of the lacrimal fluid (mm) determined by the following equation.

Increment of lacrimal fluid (mm)

$$=[SM(D-T)-SM(D-0)]-[SM(V-T)-SM(V-0)]$$

SM(D-T): Schirmer value in the eye to which the drug was administered ^{left} (right eye) T hours after administering the drug

SM(D-0): Schirmer value in the eye to which the drug was administered ^{left} (right eye) before administering the drug

SM(V-T): Schirmer value in the eye to which the vehicle was administered ^{right} (left eye) T hours after administering the vehicle

SM(V-0): Schirmer value in the eye to which the vehicle was administered ^{right} (left eye) before administering the vehicle

As examples of test results, Table 1 shows increments of the lacrimal fluid (mm) one hour after instilling solutions of test drugs (rat α -ANP, rat BNP-32 and human CNP-22; all of them were purchased from Peptide Research Institute).

Claims

1. Eyedrops for promoting lacrimal secretion containing a natriuretic peptide as an active ingredient. *in an ophthalmic vehicle*
2. Eyedrops for treating a keratoconjunctival disorder containing a natriuretic peptide as an active ingredient. *in an ophthalmic vehicle*
3. The eyedrops for treating the keratoconjunctival disorder as claimed in claim 2, wherein the keratoconjunctival disorder is at least one selected from dry eye, corneal erosion and corneal ulcer.

Specification

Eyedrops for Promoting Lacrimal Secretion or Treating Keratoconjunctival Disorders Containing Natriuretic Peptide as Active Ingredient

Technical Field

The present invention relates to eyedrops for promoting lacrimal secretion or treating keratoconjunctival disorders containing a natriuretic peptide as an active ingredient.

Background Art

A lacrimal fluid, which has a mechanism to retain wettability on living bodies, covers cornea and conjunctiva (keratoconjunctiva), retains wettability and prevents them from drying. The lacrimal fluid works as a lubricant protecting the keratoconjunctiva from stimulation by blinking and contributes to retaining smoothness of the corneal surface. The lacrimal fluid has bacteriostasis, prevents infection from bacteria, fungus, virus and the like, supplies oxygen and a variety of nutrition to the cornea and removes a carbon dioxide gas and metabolites. When the keratoconjunctiva is disordered, the lacrimal fluid plays a role to dilute and remove disordering stimuli, and works to carry liquid components such as epidermal growth factors participating in wound healing and hematocyte components such as fibronectin to disordered sites. That is, the lacrimal fluid participates in adjusting wound healing as well as retaining keratoconjunctival epithelial cells. Thus, it is known that the lacrimal fluid, though its amount is very

small, adjusts a physiological condition of the keratoconjunctiva, and thereby maintaining transparency and homeostasis of the cornea (*Journal of the Eye*, 11, 1179-1185 (1994)).

Known methods of treating keratoconjunctival disorders such as dry eye (keratoconjunctivitis sicca and the like) are a method of supplying lacrimal fluid components with artificial tears, a method of retaining a lacrimal fluid remaining on the keratoconjunctiva surface with a viscoelastic substance to lead to treating the keratoconjunctiva and the like. Since the lacrimal fluid exhibits the above-mentioned effect of curing the keratoconjunctival disorders, it is expected that finding compounds acting on a lacrimal gland function directly and promoting lacrimal secretion is useful for curing corneal erosion, corneal ulcer and the like having keratoconjunctival epithelial disorders such as dry eye.

Peptides belonging to natriuretic peptides are widely distributed in mammal, birds, amphibians and fish and are classified into three groups, namely atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptides (CNP), according to structure. Known atrial natriuretic peptides (ANP) are α -ANP consisting of 28 amino acids, α -ANP [4-28] consisting of 4th to 28th amino acids of α -ANP, α -ANP [5-28] consisting of 5th to 28th amino acids of α -ANP, β -ANP having an antiparallel dimer structure of α -ANP, high-molecular type γ -ANP having molecular weight of 13,000 formed by cutting out a signal peptide from an ANP precursor and the like. Known brain natriuretic peptides (BNP) are BNP-26 consisting of 26 amino acids, BNP-32 consisting of 32 amino acids, BNP-45 consisting of 45 amino acids, high-molecular type γ -BNP having

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molecular weight of about 13,000 formed by cutting out a signal peptide from a BNP precursor and the like. Known C-type natriuretic peptides (CNP) are CNP-22 consisting of 22 amino acids, CNP-53 consisting of 53 amino acids extending to the N-terminal and the like. These natriuretic peptides act on kidneys, adrenal glands and vascular walls and play an important role in adjusting electrolytes in a general body fluid and blood pressure ("Peptides Adjusting Circulation and Related Diseases", p. 14-25, Youdosha, 1992).

α -ANP has a vasodilatory action and a diuretic action and is used as a therapeutic agent for cardiovascular diseases such as heart failure (Jpn. Pharmacol. Ther., 23, 949-952 (1995)).

In an ophthalmological field, it was reported that α -ANP exhibits an effect of lowering intraocular pressure (Curr. Eye Res., 6, 1189-1196 (1987)). However, other effects of α -ANP have scarcely been studied, and there have been no literature which reports effects of the natriuretic peptides on lacrimal gland and the keratoconjunctival disorders by instilling them.

Few application studies of the natriuretic peptides to the ophthalmological field have been done except for the study on the effect of lowering intraocular pressure. It is a very interesting subject to study new effects of the natriuretic peptides in the ophthalmological field.

Disclosure of the Invention

Studying precisely in order to find new effects of natriuretic peptides in an ophthalmological field, the present inventors found that the natriuretic peptides exhibit effects of promoting lacrimal secretion and are useful as therapeutic agents for keratoconjunctival disorders.

The present invention relates to eyedrops for promoting the lacrimal secretion and treating the keratoconjunctival disorders containing the natriuretic peptide as an active ingredient.

The natriuretic peptides are atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptides (CNP) in the present invention. ANP, BNP and CNP having different structures are known, and the natriuretic peptides of the present invention include all of them.

The natriuretic peptides are useful drugs as therapeutic agents for cardiovascular diseases, but few effects have been reported other than their effects of lowering intraocular pressure in an ophthalmological field.

Studying application of the natriuretic peptides to the ophthalmological field, the present inventors found that when the natriuretic peptides are instilled into rabbits, the natriuretic peptides exhibit excellent effects of promoting the lacrimal secretion. Details will be described in the part of "Pharmacological Test". Since the lacrimal fluid exhibits the effect of curing the keratoconjunctival disorders as described in detail in the part of "Background Art", the present drugs are expected to be useful as the therapeutic agents for the keratoconjunctival disorders. Typical examples of the keratoconjunctival disorder are dry eye, corneal erosion and corneal ulcer.

The eyedrops of the present invention can be prepared by dissolving the natriuretic peptide in a general ophthalmic vehicle in using the eyedrops. The eyedrops can be formulated by adding optionally a suitable amount of an isotonic agent such as sodium chloride or concentrated glycerin, a buffer such

as sodium phosphate or sodium acetate, a surfactant such as polyoxyethylene sorbitan monooleate, polyoxyl 40 stearate or polyoxyethylene hydrogenated castor oil, a stabilizer such as sodium citrate or disodium edetate, a preservative such as benzalkonium chloride or parabens or the like. pH can be in the range acceptable to ophthalmic preparations and is preferably in the range of 4 to 8.

A concentration of the active ingredient in the eyedrops is 0.001 to 1% (W/V), preferably 0.005 to 0.5% (W/V), more preferably 0.05 to 0.5% (W/V). The eyedrops are administered by instilling one to several times per day.

Best Mode for Carrying out the Invention

Formulation Example and Pharmacological Test are shown below as Examples.

1. Formulation Example

Typical formulation is shown below.

Formulation 1 (Preparation of 0.1% eyedrops)

A natriuretic peptide (100 mg) was dissolved in physiological saline (100 ml) to prepare 0.1% eyedrops.

Further, varying the amount of the natriuretic peptide to be added, natriuretic peptide eyedrops having concentrations of 0.001%, 0.005%, 0.01%, 0.05%, 0.5% and 1.0% (W/V) were also prepared.

2. Pharmacological Test

The Schirmer test paper method, which is used for measurement of an amount of a human lacrimal fluid, is one method of measuring a change in an amount of a lacrimal fluid of a normal animal in instilling a drug. In

the present invention, an amount of a lacrimal fluid in instilling the natriuretic peptide was measured by using the Schirmer test paper method, and an effect of the natriuretic peptide on a rate of lacrimal secretion was studied.

Experimental method

Laboratory animal

Male Japanese white rabbits, body weight; 1.8 to 2.2 kg, were used for the experiment.

Preparation of solution of test drug

The natriuretic peptide (0.56 mg) was dissolved in sterile purified water to prepare a 0.1% solution just before using. This solution is referred to as a solution of a test drug.

Method of administering drug

The solution of the test drug (50 μ l) was instilled into a left eye once. In order to study an effect of a vehicle (purified water) on the lacrimal secretion, the vehicle alone (50 μ l) was instilled into a right eye once.

Method of measurement

Amounts of the lacrimal fluid were measured using Schirmer test paper with respect to the eye to which the drug was administered and the eye to which no drug was administered before administering the drug and after a prescribed period of time from the instillation. One end of the Schirmer test paper was folded, and the folded end was inserted into a site of one third of palpebrae inferior toward a temporal side of the rabbit. One minute later, length of a wet portion (Schirmer value, mm) of the test paper

was measured from the fold.

Three minutes before measuring the amount of the lacrimal fluid, a 0.4% ophthalmic solution of oxybuprocaine hydrochloride ($10 \mu\text{l}$), which is a local anesthetic, was instilled into both eyes once.

Results

The action of the solution of the test drug on the rate of the lacrimal secretion at a time of T hours after the instillation is represented by the increment of the lacrimal fluid (mm) determined by the following equation.

$$\begin{aligned} &\text{Increment of lacrimal fluid (mm)} \\ &= [\text{SM(D-T)} - \text{SM(D-0)}] - [\text{SM(V-T)} - \text{SM(V-0)}] \end{aligned}$$

SM(D-T): Schirmer value in the eye to which the drug was administered (right eye) T hours after administering the drug

SM(D-0): Schirmer value in the eye to which the drug was administered (right eye) before administering the drug

SM(V-T): Schirmer value in the eye to which the vehicle was administered (left eye) T hours after administering the vehicle

SM(V-0): Schirmer value in the eye to which the vehicle was administered (left eye) before administering the vehicle

As examples of test results, Table 1 shows increments of the lacrimal fluid (mm) one hour after instilling solutions of test drugs (rat α -ANP, rat BNP-32 and human CNP-22; all of them were purchased from Peptide Research Institute).

Table 1

Measuring time	Increment of lacrimal fluid (mm)		
	Rat α -ANP	Rat BNP-32	Human CNP-22
One hour after administering drug	+1.92	+2.08	+1.33

The values in the table are respective averages of six samples per group.

As apparent from Table 1, the test drugs (rat α -ANP, rat BNP-32 and human CNP-22) exhibit excellent effects of promoting the lacrimal secretion.

Industrial Applicability

The present invention can provide eyedrops containing a natriuretic peptide which exhibit an excellent effect of promoting lacrimal secretion and are useful as lacrimal secretion promoters and as therapeutic agents for keratoconjunctival disorders.

Claims

1. Eyedrops for promoting lacrimal secretion containing a natriuretic peptide as an active ingredient.
2. Eyedrops for treating a keratoconjunctival disorder containing a natriuretic peptide as an active ingredient.
3. The eyedrops for treating the keratoconjunctival disorder as claimed in claim 2, wherein the keratoconjunctival disorder is at least one selected from dry eye, corneal erosion and corneal ulcer.

Abstract

An object of the present invention is to find new effects of natriuretic peptides in an ophthalmological field. The present invention provides eyedrops for promoting lacrimal secretion or for treating keratoconjunctival disorders containing the natriuretic peptide as active ingredient. The natriuretic peptides are atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptides (CNP). Typical examples of the keratoconjunctival disorder are dry eye, corneal erosion and corneal ulcer.

APPLICATION FOR UNITED STATES LETTERS PATENT

PCT Declaration and Power of Attorney (35 U.S.C. 371(c)(4))

PCT Application - United States Designated Office

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Eyedrops for Promoting Lacrimal Secretion or Treating Keratoconjunctival Disorders Containing Natriuretic Peptide as Active Ingredient
described and claimed in International Application number PCT/JP99/05239 filed Sep. 24, 1999, and, if it was amended, as amended on

I have reviewed and understand the contents of said specification, including claims.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I claim priority benefits under 35 USC §119 of: (i) any foreign application(s) for patent or inventor's certificate listed below; or (ii) any United States provisional application(s) listed below; and have also identified below any foreign application(s) for patent or inventor's certificate, or PCT international application having a filing date before that of the application(s) on which priority is claimed.

COUNTRY	APPLICATION NUMBER	DATE (day, month, year)	PRIORITY CLAIMED
JAPAN ✓	10-273332 ✓	28, 09, 1998 ✓	yes <u>X</u> no _____
			yes _____ no _____

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I appoint the following attorneys to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith: Leonard Holtz, Reg. No. 22,974; Herbert Goodman, Reg. No. 17,081; Thomas Langer, Reg. No. 27,264; Marshall J. Chick, Reg. No. 26,853; Richard S. Barth, Reg. No. 28,180; Douglas Holtz, Reg. No. 33,902; and Robert P. Michal, Reg. No. 35,614.

CORRESPONDENCE AND CALLS TO:

FRISHAUF, HOLTZ, GOODMAN, LANGER & CHICK, P.C.
767 Third Avenue - 25th Floor Tel.: (212) 319-4900
New York, New York 10017-2023 Fax.: (212) 319-5101

INVENTOR: SIGNATURE

DATE

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Sign: <u>Katsuhiko Nakata</u> Type: <u>Katsuhiko NAKATA</u>	Date: <u>Mar. 23, 2001</u> Citizen of: <u>JAPAN</u>	Residence: (City & Country) <u>Ikoma-shi, Japan JPX</u> Post Office Address: c/o SANTEN PHARMACEUTICAL CO., LTD., KENKYUSHO, 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101 Japan
Sign: <u>Masatsugu Nakamura</u> Type: <u>Masatsugu NAKAMURA</u>	Date: <u>Mar. 23, 2001</u> Citizen of: <u>JAPAN</u>	Residence: (City & Country) <u>Ikoma-shi, Japan JPX</u> Post Office Address: c/o SANTEN PHARMACEUTICAL CO., LTD., KENKYUSHO, 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101 Japan
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